Food and Drug Administration (FDA)
Center for Drug Evaluation and Research (CDER)

Psychopharmacologic Drugs Advisory Committee

October 25, 2005

Questions to the Committee

We have developed a list of questions that we would like the committee to address during the discussion phase of the meeting. For purposes of simplifying the discussion, we will focus the initial questions (Questions 1 through 8) on Major Depressive Disorder (MDD), and then return later to expand the questions to any chronic psychiatric disorder. [Note: We are asking for a vote on questions 1 and 2, while for others, discussion and comments would suffice.]

1. Is it a reasonable expectation that a sponsor would have accumulated data for both acute and longer-term efficacy trials at the time of filing of an application for a drug for the treatment of MDD? **[Vote requested]**

2. If the answer to question 1 is yes, is it a reasonable expectation that the sponsor must have demonstrated both acute and longer-term efficacy for MDD? **[Vote requested]**

   For those voting No on this question, 2 additional questions [Note: When asking for longer-term trials as a phase 4 commitment at the time of approval of an acute claim, it has been our standard to request a single longer-term trial. In the one situation where a sponsor submitted an application based only on longer-term data, we required 2 positive longer-term trials to support the claim.]:
   a. If the acute studies support an acute claim, but the longer-term trial fails to demonstrate an effect, could the drug be approved for short-term use, with a mention of the negative longer-term findings in the label? **[Vote requested]**

   b. If the longer-term studies support a maintenance claim, but the acute trials fail to demonstrate an effect, could the drug be approved for maintenance treatment, with a mention of the negative acute findings in the label? [Note: We have, in fact, already approved a drug for maintenance treatment in the absence of acute efficacy, i.e., Lamictal for bipolar maintenance, however, without mention of the negative acute findings in the label.] **[Vote requested]**

3. If the answer to question 1 is yes, at what point in a development program for a drug for MDD should this new requirement for longer-term data at the time of filing of an application be implemented? **[Discussion requested]**

4. What is the minimum period of time that patients with MDD should remain in a responder status before being randomized in a randomized withdrawal study? An extension to this question is whether or not this duration should be different depending on whether this is a monotherapy or an add-on maintenance trial? **[Discussion requested]**

5. Would it be reasonable to accept minor and temporary excursions above criterion scores for "responder" status for MDD patients in an open run-in phase, or minor dosage adjustments, and still consider such patients to have remained in a "responder" status? **[Discussion requested]**

6. Would it be reasonable to accept minor and temporary excursions above criterion scores for MDD patients in the randomized phase, and even slight dose adjustments, without considering such patients to have relapsed? **[Discussion requested]**

7. Should placebo responders during a double-blind phase of an acute trial, who are switched to active drug during a continuation phase, be considered for randomization in a randomized withdrawal trial, i.e., should they be considered similar to (or different from) patients who responded on active drug and were then continued on active drug for longer-term stabilization? **[Discussion requested]**

8. Should sponsors be encouraged (or even required) to utilize fixed dose randomized withdrawal studies rather than randomizing MDD patients to their optimal dose during the run-in phase? **[Discussion requested]**

9. Would the answers to any of the questions change in considering other chronic psychiatric disorders? **[Discussion requested: Note—It isn't necessary or possible to discuss every chronic psychiatric disorder at this one-day meeting. Rather, we are trying to get a sense of whether or not, if you agree with a requirement for longer-term data, that requirement should be applied generally to all chronic psychiatric disorders. If not, what are the exceptions to the rule? In addition, should the course of long-term illness (e.g., chronic with discrete episodes, cyclical, or persistent symptoms) determine the specific design of the longer-term trial needed to show longer-term efficacy?]**

10. Are there alternative designs that should be considered for establishing longer-term efficacy [Note: We are happy to consider discussion of the suggestion of active-controlled comparisons in longer-term trials for schizophrenia, however, until more data are accumulated and presented, we are not likely to consider this issue ripe for resolution.]? **[Discussion requested]**

11. Information about longer-term efficacy from such a trial is generally located in 3 different sections of labeling: (1) Clinical Trials, under Clinical Pharmacology; (2) Indications and Use; and (3) Dosage and Administration. To illustrate what is the division's current approach to including this kind of information in labeling, we have included here language from these sections of labeling for the drug Zyprexa:

Clinical Pharmacology/Clinical Trials

Bipolar Disorder
(3) In another trial, 361 patients meeting DSM-IV criteria for a manic or mixed episode of bipolar disorder who had responded during an initial open-label treatment phase for about two weeks, on average, to olanzapine 5 to 20 mg/day were randomized to either continuation of olanzapine at their same dose (n=225) or to placebo (n=136), for observation of relapse. Approximately 50% of the patients had discontinued from the olanzapine group by day 59 and 50% of the placebo group had discontinued by day 23 of double-blind treatment. Response during the open-label phase was defined by having a decrease of the Y-MRS total score to $\leq$ 12 and HAM-D 21 to $\leq$ 8. Relapse during the double-blind phase was defined as an increase of the Y-MRS or HAM-D 21 total score to $\geq$ 15, or being hospitalized for either mania or depression. In the randomized phase, patients receiving continued olanzapine experienced a significantly longer time to relapse.

Indications and Usage

Bipolar Disorder
Maintenance Monotherapy — The benefit of maintaining bipolar patients on monotherapy with oral ZYPREXA after achieving a responder status for an average duration of two weeks was demonstrated in a controlled trial (see Clinical Efficacy Data under CLINICAL PHARMACOLOGY). The physician who elects to use ZYPREXA for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

Dosage and Administration

Bipolar Disorder
Maintenance Monotherapy — The benefit of maintaining bipolar patients on monotherapy with oral ZYPREXA at a dose of 5 to 20 mg/day, after achieving a responder status for an average duration of two weeks, was demonstrated in a controlled trial (see Clinical Efficacy Data underCLINICAL PHARMACOLOGY). The physician who elects to use ZYPREXA for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

Is this language a reasonable interpretation and translation of the data from the longer-term trial that supported the longer-term claim for Zyprexa in bipolar disorder, or is there a better way of presenting this information in labeling? **[Discussion requested]**

12. If there are data supporting a longer-term claim for adults for a drug for a chronic psychiatric indication, is there a need to obtain longer-term data for a pediatric indication for this same disorder, or would it be sufficient to obtain acute data for the pediatric population and extrapolate from adult data for the longer-term claim? **[Discussion requested]**